Amendments to the Speecification begin on page 3 of this paper.

Amendments to the Claims begin on page 7 of this paper.

Remarks begin on page 13 of this paper.

Amendments to the Specification:

Please replace the paragraph beginning at page 6, line 28, with the following:

A1

--Figure 1 presents the nucleotide and amino acid sequence of factor X ~~(Seq.ID NO. 1 and 2)~~ (SEQ ID NOS:1 and 2).--

Please replace the paragraph beginning at page 6, line 30, with the following:

A2

--Figure 2 is a diagrammatic representation of the factor X analog with a modified protease cutting site in the region of the activation peptide (SEQ ID NOS:7-9).--

Please replace the paragraph beginning at page 7, line 24, with the following:

A3

--The amino acid modification in this region creates a new recognition and processing site for factor XIa or a derivative thereof, which site does not naturally occur in this position in the polypeptide. Factor XIa or a derivative thereof does not normally cleave Fx in the region of Glu-Arg-Gly-Asp-Asn-Asp-Phe-Thr-Arg/Ile (SEQ ID NO:10) of amino acids 226-234. Surprisingly, the factor X analog according to the present invention has an at least 2-fold, preferably an at least 5-fold, and especially an at least 10-fold increased ability to be activated by factor XIa compared to the factor X analog according to WO 98/38317.--

Please replace the paragraph beginning at page 8, line 24, with the following:

A4

--The invention makes available factor X analogs which are modified in the activation peptide relative to the naturally occurring factor X sequence and which have a changed protease specificity. Amino acid Modifications may take place in position Ile235 (R1), Arg234, Thr233

(R2), Leu 232 (R3), Asn231 (R4), Asn230 (R5), Asp229 (R6), Gly228 (R7), and ~~Arg229~~ Arg227 (R8), while Arg234, however, preferably remains unchanged.--

Please replace the paragraph beginning at page 9, line 15, with the following:

--Embodiments of the factor X analogs according to the present invention to be preferred are FX analogs which are modified as follows:

a) R1 = Val, R2= Thr, R3 = Leu, R4 = Asp, R5 = Asn, R6 = Asp, R7 = Ser, and R8 = Gln (SEQ ID NO:11) and which are processed by means of factor XIa or a derivative thereof;

b) R1 = Ile, R2 = Thr, R3 = Leu, R4 = Asp, R5 = Asn, R6 = Asp, R7 = Ser, and R8 = Gln (SEQ ID NO:12) and which are processed by means of factor XIa or a derivative thereof (Figure 2);

A5

c) R1 = Val, R2 = Thr, R3 = Leu, R4 = Lys, R5 = Ser, R6 = Thr, R7 = Gln, and R8 = Ser (SEQ ID NO:13) and which are processed by means of factor XIa or a derivative thereof; and

d) R1 = Ile, R2 = Thr, T3 = Leu, R4 = Lys, R5 = Ser, R6 = Thr, R7 = Gln, and R8 = Ser (SEQ ID NO:14) and which are processed by means of factor XIa or a derivative thereof.--

Please replace the paragraph beginning at page 22, line 12, with the following:

--The cDNA of FX was isolated from a human liver lambda-cDNA bank as described by Messier et al. (Gene 99 (1991), pp. 291-294). By means of PCR, using oligonucleotide #2911 (5'-ATTACTCGAGAAGCTTACCATGGGGCGCCCACTG-3') ~~(SEQ ID No. 3)~~ (SEQ ID NO:3) as the 5' primer and oligonucleotide #2912

A6

(5'-ATTACAATTGCTGCAGGGATCCAC-3') ~~(SEQ.ID No. 4)~~ (SEQ ID NO:4) as the 3' primer, a DNA fragment was amplified from a positive clone, which DNA fragment contains the 1,457 kB FX-coding sequence and 39 bp of the 3' nontranslated region, flanked by an XhoI cutting site on the 5' end and an MfeI cutting site on the 3' end. In addition, by means of primer #2911, the sequence ACC was inserted in front of ATG of FX, thus ensuring that an optimum Kozak

translation initiation sequence forms. Subsequently this PCR fragment was cloned as XhoI/MfeI fragment into the expression vector phAct which had been cut with SalI an EcoRI. The expression factor phAct comprises approximately 3.3 kb of the promoter, 78 bp of 5' UTR, and the approximately 1 kb measuring intron of the human beta-actin gene (Fischer et al., FEBS Lett. 351 (1994), pp. 345-348), a multiple cloning cutting site and the SV40 polyadenylation site. The resulting expression plasmid was called phAct-rFX.--

Please replace the paragraph beginning at page 22, line 31, with the following:

--To produce recombinant FX/FXIa (Q-R/I) analogs, the amino acid sequence from position 227 to 234 (Arg-Gly-Asp-Asn-Asn-Leu-Thr-Arg/Ile; SEQ ID NO:15) which serves to activate FX into FXa was replaced with the intrinsic tenase complex FIXa/FVIIIa or by the extrinsic FVIIa/TF complex, by the sequence Gln-Ser-Phe-Asn-Asp-Phe-Thr-Arg/Ile (hereinafter referred to as (Q-R/I)), specifically activated by means of the coagulation factor XIa (Figure 2). Q-R was prepared in conformity with the second FXIa cutting site, such as it is present in the 'natural' substrate FIX. The expression plasmid for this rFX analog is derived from plasmid phAct/rFX. For cloning purposes, the HindIII-NaeI DNA fragment from the phAct-rFX expression plasmid which comprises the FX-coding region from position +1 to +1116 was inserted into the HindIII-SmaI restriction cutting sites of plasmid pUC19. The resulting plasmid was called pUC/FX. This made it possible for the FX sequence of nucleotide 508 to 705 which corresponds to amino acids 160 to 235 to be removed from the pUC/FX plasmid via Bsp120I and BstXI restriction cuts and to be replaced by a mutated FX-DNA fragment. The mutated DNA fragment contains the FX-exogenic cleavage site for FXIa, instead of the FIXa/FVIIIa and FVIIa/TF site, and is produced by means of PCR. Plasmid phAct/rFX serves as a model for the PCR. To produce the
Gln-Ser-Phe-Asn-Asp-Phe-Thr-Arg/Ile (SEQ ID NO:16) (Q-R/I) cleavage site, oligonucleotide #4211 (5'-GGCAAGGCCTGCATTCCCACA-3') ~~(SEQ ID. No. 5)~~ (SEQ ID NO:5) is used as the 5' primer and oligonucleotide #5039

A7

(5'-GCGCTCCCACGATCCTGGTGAAGTCATTAAAGCTTTGCTCAGGCTGCGTCTGGTT-3') ~~(SEQ ID No. 6)~~ (SEQ ID NO:6) is used as the 3' primer. Therefore, amino acids Arg, Gly, Asp, Asn, and Leu are replaced in positions 227, 228, 229, 231, and 232 with Gln, Ser, Phe, Asp, and Phe. The PCR product is recut with Bsp120I and BstXI and inserted into the pUC-FX plasmid that had been opened with Bsp120I/BstXI. Subsequently, the DNA fragment which contains the new cleavage site is reinserted via HindIII/AgeI into phact-FX which had been cut with the same restriction enzymes. The resulting plasmid is called phAct-FX/FXIa (Q-R/I).--

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 8, at the end of the application.